Unexpected role of two lipid-binding mitochondrial proteins associated with heart disease and diabetes

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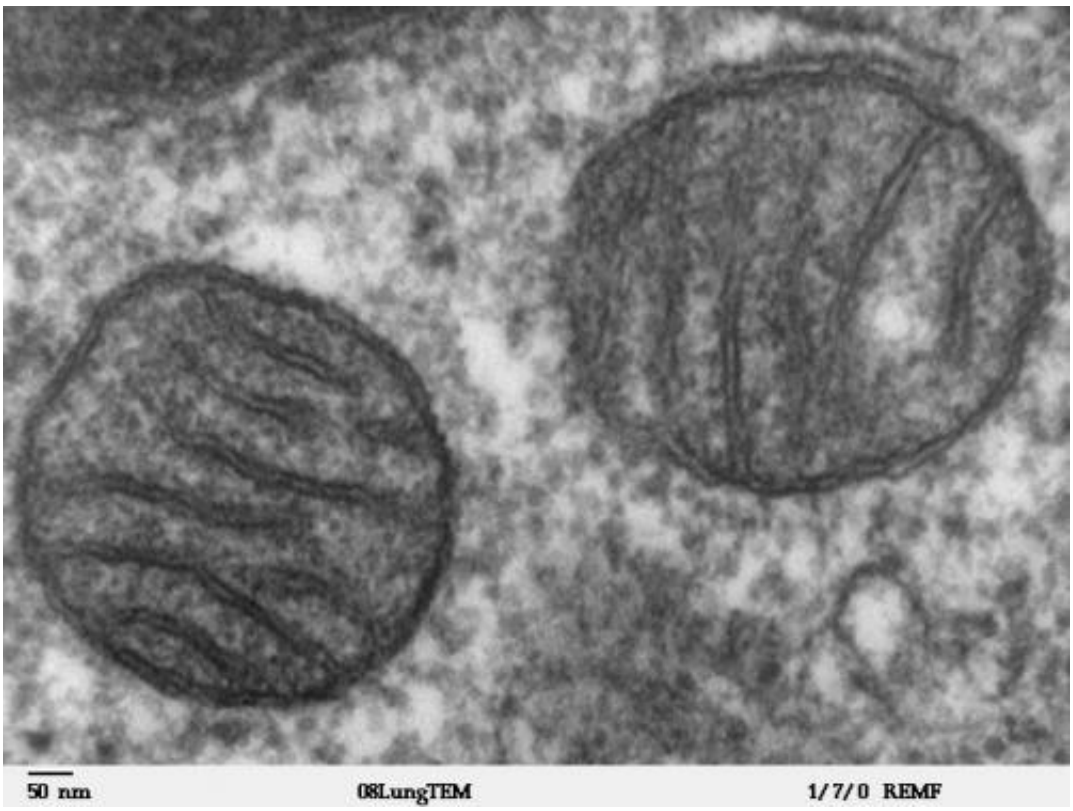

Mitochondria. Credit: Wikipedia commons

Mitochondria are the powerhouse of cells, continuously converting energy from food into the chemical energy currency called ATP. This essential process depends on large protein complexes within the inner

membrane of mitochondria acting similar to batteries. A new study led by Dr. Ruchika Anand and Prof. Andreas Reichert, Heinrich-Heine-University Duesseldorf, has found that two lipid-binding proteins located inside of mitochondria control their overall stability. This was further shown to be linked to a unique mitochondrial lipid and its synthesis: cardiolipin. Increased build-up of a sugar-modified form of MIC26 was earlier found in blood plasma of the patients suffering from diabetic cardiomyopathy. This study provides the first link between mitochondrial structure, lipids and assembly of large respiratory protein units of mitochondria and their importance in diabetes and heart diseases.

Fat- or lipid-binding proteins called apolipoproteins are well known to bind to lipids (e.g., phospholipids and cholesterol) and to mediate formation of lipoproteins (e.g. HDL or LDL). The main function of lipoproteins is to transport lipids in the blood. They take part in uptake, clearance and distribution of all lipids in an organism. Several classes of these proteins are found with different functions. Surprisingly, two apolipoproteins (Apolipoprotein O (APOO/MIC26) and Apolipoprotein O-like (APOOL/MIC27) were earlier found at a location distinct from the blood, namely in mitochondria, and were associated with a large protein assembly called the MICOS complex. Apolipoprotein O (MIC26) occurs in two forms, a sugar-bound and a non-sugar-bound form. While the non-sugar-bound form is present inside the mitochondria, the sugar-bound form is found in the blood plasma. Increased quantity of the sugar-bound form in blood plasma was interestingly associated with diabetes and diabetic cardiomyopathy. A mutation in APOO/MIC26 is associated with mitochondrial myopathy, lactic acidosis, cognitive impairment and autistic features.

The research groups determined the function of these apolipoproteins. They found that the cooperation of the two apolipoproteins of mitochondria (APOO/MIC26 and APOOL/MIC27) are required for the

global stability of major mitochondrial protein complexes involved in energy conversion by oxidative phosphorylation. These mitochondrial complexes are arranged in large assemblies so that they can work properly and efficiently to convert the energy from the food into the chemical energy in the form of ATP.

The internal structure of mitochondria is arranged to accommodate these batteries in the cristae, folds of the inner membrane. APOO/MIC26 and APOOL/MIC27 cooperate to form proper mitochondrial structure including tubular structures located at the entry point of cristae termed crista junctions. The study revealed that both proteins are required to maintain the correct levels of the mitochondrial specific lipid cardiolipin. The scientists found that simultaneous deletion of APOO/MIC26 and APOOL/MIC27 in a cell cause major disturbances in cellular respiration together with the occurrence of abnormal mitochondrial structure. This study exemplifies the importance of mitochondrial membrane structures and large protein assemblies in diseases such as diabetic cardiomyopathy and mitochondrial myopathy. This could lead to further insights for medical therapies. The work was published after peer review in *Life Science Alliance*.

More information: Ruchika Anand et al, MIC26 and MIC27 cooperate to regulate cardiolipin levels and the landscape of OXPHOS complexes, *Life Science Alliance* (2020). DOI: 10.26508/lsa.202000711

Provided by Heinrich-Heine University Duesseldorf

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